Search by STIC 10/688,495 priority 3/2/89

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=> fil reg
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         0.21       0.21

FILE 'REGISTRY' ENTERED AT 15:02:26 ON 31 MAR 2006
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STRUCTURE FILE UPDATES:   29 MAR 2006  HIGHEST RN 878540-28-4
DICTIONARY FILE UPDATES:  29 MAR 2006  HIGHEST RN 878540-28-4

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* the IDE default display format and the ED field has been added,    *
* effective March 20, 2005.  A new display format, IDERL, is now     *
* available and contains the CA role and document type information.  *
*                                                                    *
**********************************************************************

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predicted properties as well as tags indicating availability of
experimental property data in the original document.  For information
on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

=> e interleukin 4/cn 5
E1            1     INTERLEUKIN 32 (HUMAN ISOFORM B)/CN
E2            1     INTERLEUKIN 32 (HUMAN ISOFORM Δ)/CN
E3            0 --> INTERLEUKIN 4/CN
E4            1     INTERLEUKIN 4 (11-ALANINE,121-ASPARTIC ACID,124-ASPARTIC ACI
                    D)(HUMAN CLONE 46)/CN
E5            1     INTERLEUKIN 4 (12-ALANINE,121-ASPARTIC ACID,124-ASPARTIC ACI
                    D)(HUMAN CLONE 46)/CN

=> s interleukin 4 ?/cn
L1          243 INTERLEUKIN 4 ?/CN

=> e interleukin 4 receptor/cn
E1            1     INTERLEUKIN 4 ALPHA-CHAIN PRECURSOR (HUMAN CHROMOSOME 16 CLO
                    NE 582J2 )/CN
E2            1     INTERLEUKIN 4 ALPHA-CHAIN PRECURSOR (HUMAN CLONE 582J2)/CN
E3            0 --> INTERLEUKIN 4 RECEPTOR/CN
```

```
E4            1      INTERLEUKIN 4 RECEPTOR (CANIS FAMILIARIS)/CN
E5            1      INTERLEUKIN 4 RECEPTOR (EQUUS CABALLUS GENE IL4R A-CHA
                     IN PRECURSOR)/CN
E6            1      INTERLEUKIN 4 RECEPTOR (EQUUS CABALLUS GENE IL4R SOLUBLE ISO
                     FORM PRECURSOR)/CN
E7            1      INTERLEUKIN 4 RECEPTOR (EQUUS CABALLUS SPLICE VARIANT)/CN
E8            1      INTERLEUKIN 4 RECEPTOR (EQUUS CABALLUS)/CN
E9            1      INTERLEUKIN 4 RECEPTOR (FELIS CATUS FRAGMENT)/CN
E10           1      INTERLEUKIN 4 RECEPTOR (HUMAN A-SUBUNIT N-TERMINAL FRA
                     GMENT) FUSION PROTEIN WITH PEPTIDE (STREPTAVIDIN TAG)/CN
E11           1      INTERLEUKIN 4 RECEPTOR (HUMAN 197-AMINO ACID FRAGMENT)/CN
E12           1      INTERLEUKIN 4 RECEPTOR (HUMAN CLONE 2674 SUBUNIT A PRE
                     CURSOR N-TERMINAL FRAGMENT) FUSION PROTEIN WITH INTERLEUKIN
                     13 RECEPTOR (HUMAN FRAGMENT) FUSION PROTEIN WITH IMMUNOGLOBU
                     LIN G1 (HUMAN .GAMMA/CN

=> s interleukin 4 receptor ?/cn
L2            62 INTERLEUKIN 4 RECEPTOR ?/CN

=> fil medl,biosis,embase,caplus;s (l1 or interleukin 4 or histocompatibility
antigens class ii or mcgf2 or mast cell growth factor or bcgf1 or bsf or b
cell(w)(stimulatory or growth)(w)factor? or binetrakin)
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                      11.28      11.49

FILE 'MEDLINE' ENTERED AT 15:04:37 ON 31 MAR 2006

FILE 'BIOSIS' ENTERED AT 15:04:37 ON 31 MAR 2006
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FILE 'EMBASE' ENTERED AT 15:04:37 ON 31 MAR 2006
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FILE 'CAPLUS' ENTERED AT 15:04:37 ON 31 MAR 2006
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L3         33794 FILE MEDLINE
L4         27091 FILE BIOSIS
L5         26198 FILE EMBASE
L6         22783 FILE CAPLUS

TOTAL FOR ALL FILES
L7        109866 (L1 OR INTERLEUKIN 4 OR HISTOCOMPATIBILITY ANTIGENS CLASS II OR
                 MCGF2 OR MAST CELL GROWTH FACTOR OR BCGF1 OR BSF OR B CELL(W)(ST
                IMULATORY OR GROWTH)(W) FACTOR? OR BINETRAKIN)

=> s l7 or il-4
L8         42794 FILE MEDLINE
L9         32534 FILE BIOSIS
L10        29170 FILE EMBASE
L11        27786 FILE CAPLUS

TOTAL FOR ALL FILES
L12       132284 L7 OR IL-4
```

```
=> s l2 or interleukin 4 receptor or il-4(w)(r or receptor) or cd124 antigen
L13         879 FILE MEDLINE
L14        1356 FILE BIOSIS
L15        1383 FILE EMBASE
L16        1548 FILE CAPLUS

TOTAL FOR ALL FILES
L17        5166 L2 OR INTERLEUKIN 4 RECEPTOR OR IL-4(W)(R OR RECEPTOR) OR CD124
                ANTIGEN

=> s (antibod? or monoclonal antibod? or mab) and l12 and l17
L18         261 FILE MEDLINE
L19         271 FILE BIOSIS
L20         435 FILE EMBASE
L21         484 FILE CAPLUS

TOTAL FOR ALL FILES
L22        1451 (ANTIBOD? OR MONOCLONAL ANTIBOD? OR MAB) AND L12 AND L17

=> s l22 and bind?
L23          92 FILE MEDLINE
L24          78 FILE BIOSIS
L25         128 FILE EMBASE
L26         204 FILE CAPLUS

TOTAL FOR ALL FILES
L27         502 L22 AND BIND?

=> s murine and l27
L28          27 FILE MEDLINE
L29          21 FILE BIOSIS
L30          29 FILE EMBASE
L31          27 FILE CAPLUS

TOTAL FOR ALL FILES
L32         104 MURINE AND L27

=> s l32 and (amino acid or protein)
L33          19 FILE MEDLINE
L34          13 FILE BIOSIS
L35          18 FILE EMBASE
L36          19 FILE CAPLUS

TOTAL FOR ALL FILES
L37          69 L32 AND (AMINO ACID OR PROTEIN)

=> s inihibt? and l37
L38           0 FILE MEDLINE
L39           0 FILE BIOSIS
L40           0 FILE EMBASE
L41           0 FILE CAPLUS

TOTAL FOR ALL FILES
L42           0 INIHIBT? AND L37

=> dup rem l37
PROCESSING COMPLETED FOR L37
L43          30 DUP REM L37 (39 DUPLICATES REMOVED)

=> d 1-30 ibib abs ;s mosley b?/au
```

L43 ANSWER 1 OF 30 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2006132025 EMBASE Full-text
TITLE: The activity of interleukin-4 receptor α-chain promoter is regulated by a GT box element.
AUTHOR: Dorado B.; Martin-Saavedra F.M.; Jerez M.J.; Ballester S.
CORPORATE SOURCE: S. Ballester, Unidad de Regulacion Genica, Centro Nacional de Microbiologia, Instituto de Salud Carlos III, Carretera Majadahonda-Pozuelo Km 2, 28220 Madrid, Spain. sballes@isciii.es
SOURCE: Molecular Immunology, (2006) Vol. 43, No. 11, pp. 1808-1816. .
Refs: 48
ISSN: 0161-5890 CODEN: IMCHAZ
PUBLISHER IDENT.: S 0161-5890(05)00377-9
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 022 Human Genetics
026 Immunology, Serology and Transplantation
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20060331
Last Updated on STN: 20060331

AB Interleukin-4 receptor (IL-4R) is the cell surface complex through which interleukin-4 ( IL-4) signals exert its critical biological effects. The α-chain of IL-4R is responsible for the high affinity binding of IL-4. In this report, is characterized, the 5' untranslated flanking region of murine IL-4Rα gene in the Th2 clone D10.G4.1. We have analyzed a DNA fragment spanning from -995 to +84 relative to the transcription start point. Mutagenesis analysis shows that, neither the previously described Stat6 (-395) nor the NFAT (-266) and NFκB (+25) sequences localized here, are involved in the IL-4Rα promoter activity. Reporter assays demonstrate that maximum transcriptional activity is achieved by the -89 to +84 sequence and this activity is independent of a TATA-like box located at -25. We have identified a GT box located at -45 as the critical element for the IL-4Rα promoter activity. Experiments in SL2 cells, which lack endogenous Sp proteins, show that IL-4Rα minimal promoter is transactivated by proteins of Sp family. .COPYRGT. 2005 Elsevier Ltd. All rights reserved.

L43 ANSWER 2 OF 30 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN DUPLICATE 1

ACCESSION NUMBER: 2006:190143 BIOSIS Full-text
DOCUMENT NUMBER: PREV200600188657
TITLE: Identification of core functional region of murine IL-4 using peptide phage display and molecular modeling.
AUTHOR(S): Yao, Gang; Chen, Weiyan; Luo, Haibin; Jiang, Qunfeng; Xia, Zongxiang; Zang, Lei; Zuo, Jianping; Wei, Xin; Chen, Zhengjun; Shen, Xu; Dong, Chen; Sun, Bing [Reprint Author]
CORPORATE SOURCE: Chinese Acad Sci, Shanghai Inst Biol Sci, Inst Biochem Cell Biol, Mol Cell Biol Lab, 320 Yueyang Rd, Shanghai 200031, Peoples R China
xiazx@mail.sloc.ac.cn; bsun@sibs.ac.cn
SOURCE: International Immunology, (JAN 2006) Vol. 18, No. 1, pp. 19-29.
ISSN: 0953-8178.

DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 15 Mar 2006
Last Updated on STN: 15 Mar 2006

AB Murine IL-4 is a pleiotropic cytokine with undefined core functional region for eliciting downstream signaling. We used molecular modeling to predict the binding sites recognized by an anti-IL-4-neutralizing mAb (11B.11) and peptide phage display to delineate their makeup. The results of these approaches were confirmed by site-directed mutagenesis analysis. The results suggest that the amino acid residues spanning from 79 to 86 (QRLFRAFR) on IL-4 are of the major binding site for 11B.11. Furthermore, the functional experiments demonstrate that the residues R80, R83 and R86, which are located in the helix C of murine IL-4, play a crucial role in binding to the IL-4R alpha-chain. Taken together, a new core functional region of murine IL-4 is identified, which provides new insight into the interaction between IL-4 and IL-4R alpha. In addition, the results demonstrate that 11B.11 binds to a core functional region of murine IL-4, which prevents this cytokine from interacting with its cognate receptor.

L43 ANSWER 3 OF 30 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:1081081 CAPLUS Full-text
DOCUMENT NUMBER: 142:69928
TITLE: Differentially regulated hepatocellular carcinoma genes and protein and DNA arrays for use in diagnosis and drug screening
INVENTOR(S): Ren, Ee Chee; Neo, Soek Ying
PATENT ASSIGNEE(S): Agency for Science, Technology and Research, Singapore
SOURCE: PCT Int. Appl., 123 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2004108964 | A1 | 20041216 | WO 2004-SG166 | 20040604 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| EP 1631682 | A1 | 20060308 | EP 2004-736172 | 20040604 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK | | | | |

PRIORITY APPLN. INFO.: US 2003-475508P P 20030604
WO 2004-SG166 W 20040604

AB The invention provides genes differentially expressed in hepatocellular carcinoma (HCC) as well as DNA and protein arrays which may be used for HCC diagnosis, to assess HCC progression or regression, or the efficacy and/or toxicity of HCC therapeutics, and/or to identify candidate compds. for HCC therapy, with high predictive accuracy.

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L43 ANSWER 4 OF 30 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2004351389 EMBASE Full-text
TITLE: Immunomodulation: The future of allergy and asthma treatment.
AUTHOR: Bloebaum R.M.; Grant J.A.; Sur S.
CORPORATE SOURCE: Dr. J.A. Grant, University of Texas Medical Branch, Department of Internal Medicine, Allergy and Immunology Division, 301 University Boulevard, Galveston, TX 77555-1083, United States. jagrant@utmb.edu
SOURCE: Current Opinion in Allergy and Clinical Immunology, (2004) Vol. 4, No. 1, pp. 63-67. .
Refs: 38
ISSN: 1528-4050 CODEN: COACCS
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 015 Chest Diseases, Thoracic Surgery and Tuberculosis
026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20040909
Last Updated on STN: 20040909

AB Purpose of review: As the prevalence of asthma and allergic disease increases around the world, it is clear that more effective therapies and disease-modifying agents are needed. Treatment for allergic disease is evolving with an increase in understanding of the etiology. Recent findings: The first immunomodulatory treatment was recently approved for use in the United States when the Food and Drug Administration approved the use of a humanized monoclonal anti-IgE antibody in patients with allergic asthma. Another strategy that has proved effective in a murine model is the downregulation of the whole immune system by targeting adhesion molecules, which has been evaluated in a recent human trial. Other strategies for the treatment of allergic diseases concentrate on refocusing the immune system away from an allergic-type response. These include the use of targeted therapies towards specific cytokines, cytokine receptors or chemokine receptors, and the use of specific bacterial DNA sequences (unmethylated cytosine-guanine dinucleotides). Finally, attention is being focused on possible therapies that may tilt the immune response to a non-allergic response by interfering with signaling molecule pathways. Summary: Immunomodulation will play a key role in future therapies for allergic disease. These treatment modalities may not only treat allergic disease, but also be beneficial in reducing the morbidity and mortality for which it is responsible.

L43 ANSWER 5 OF 30 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:335302 CAPLUS Full-text
DOCUMENT NUMBER: 138:349702
TITLE: Selection of cells expressing heteromeric polypeptides by a co-expressing selectable marker protein as two interactable units containing leucine zipper domains
INVENTOR(S): McGrew, Jeffrey T.; Bianchi, Allison A.
PATENT ASSIGNEE(S): Immunex Corporation, USA
SOURCE: PCT Int. Appl., 28 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2003035887 | A1 | 20030501 | WO 2002-US29985 | 20020920 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| CA 2458811 | AA | 20030501 | CA 2002-2458811 | 20020920 |
| US 2003082735 | A1 | 20030501 | US 2002-251447 | 20020920 |
| EP 1434871 | A1 | 20040707 | EP 2002-768877 | 20020920 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK | | | | |
| JP 2005511031 | T2 | 20050428 | JP 2003-538387 | 20020920 |

PRIORITY APPLN. INFO.: US 2001-323954P P 20010920
WO 2002-US29985 W 20020920

AB This invention relates to the general field of recombinant expression of polypeptides in animal cell culture. More particularly, the invention concerns improved selection in cells of recombinantly engineered vectors designed to express polypeptides. Specifically, the improved selection is achieved by co-expressing selectable marker protein as two interactable units containing leucine zipper domains LZ. The exemplified marker, dihydrofolate reductase, is expressed as two sep. fragments, while the first fragment extends from amino acids 1-105 and the second fragment includes amino acids 106-187 as fusion protein (LZ-linker-DHFR) containing GCN4 leucine zipper and flexible linker. The cDNA for DHFR fragments are inserted into bicistronic vectors downstream of the IRES element which express murine anti-IL4R antibody heavy or light chain as the first part of the bicistronic gene. The invention also relates to the construction of these multicistronic gene expressing vectors which contain a truncated 600 base pair portion of the expression augmenting sequence element (EASE), CMV promoter, and polyA signal.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L43 ANSWER 6 OF 30 MEDLINE on STN
ACCESSION NUMBER: 2001410014 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 11313423
TITLE: A murine IL-4 receptor antagonist that inhibits IL-4- and IL-13-induced responses prevents antigen-induced airway eosinophilia and airway hyperresponsiveness.
AUTHOR: Tomkinson A; Duez C; Cieslewicz G; Pratt J C; Joetham A; Shanafelt M C; Gundel R; Gelfand E W
CORPORATE SOURCE: Division of Cell Biology, Department of Pediatrics, National Jewish Medical and Research Center, Denver, CO 80206, USA.
CONTRACT NUMBER: HL36577 (NHLBI)
HL61005 (NHLBI)
SOURCE: Journal of immunology (Baltimore, Md. : 1950), (2001 May 1)

Vol. 166, No. 9, pp. 5792-800.
Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200107
ENTRY DATE: Entered STN: 20010723
Last Updated on STN: 20010723
Entered Medline: 20010719

AB The closely related Th2 cytokines, IL-4 and IL-13, share many biological functions that are considered important in the development of allergic airway inflammation and airway hyperresponsiveness (AHR). The overlap of their functions results from the IL-4R alpha-chain forming an important functional signaling component of both the IL -4 and IL-13 receptors. Mutations in the C terminus region of the IL-4 protein produce IL-4 mutants that bind to the IL-4R alpha-chain with high affinity, but do not induce cellular responses. A murine IL-4 mutant (C118 deletion) protein (IL-4R antagonist) inhibited IL-4- and IL-13-induced STAT6 phosphorylation as well as IL-4- and IL-13-induced IgE production in vitro. Administration of murine IL-4R antagonist during allergen (OVA) challenge inhibited the development of allergic airway eosinophilia and AHR in mice previously sensitized with OVA. The inhibitory effect on airway eosinophilia and AHR was associated with reduced levels of IL-4, IL-5, and IL-13 in the bronchoalveolar lavage fluid as well as reduced serum levels of OVA-IGE: These observations demonstrate the therapeutic potential of IL- 4 mutant protein receptor antagonists that inhibit both IL-4 and IL-13 in the treatment of allergic asthma.

L43 ANSWER 7 OF 30 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2000080912 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 10612755
TITLE: Functional interleukin 4 receptor and interleukin 2 receptor common gamma-chain on human non-small cell lung cancers: novel targets for immune therapy.
AUTHOR: Essner R; Huynh Y; Nguyen T; Morton D L; Hoon D S
CORPORATE SOURCE: Department of Molecular Oncology, John Wayne Cancer Institute at Saint John's Health Center, Santa Monica, CA, USA.. essnerr@jwci.org
SOURCE: The Journal of thoracic and cardiovascular surgery, (2000 Jan) Vol. 119, No. 1, pp. 10-20.
Journal code: 0376343. ISSN: 0022-5223.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200002
ENTRY DATE: Entered STN: 20000229
Last Updated on STN: 20000229
Entered Medline: 20000217

AB OBJECTIVE: The interleukin 4 receptor has been demonstrated on the surface of human non-small cell lung carcinoma cell lines and tumor specimens. Interleukin 4 causes G1-phase cell-cycle arrest of non-small cell lung cancer cell lines expressing the interleukin 4 receptor; the effect directly correlates with the expression of the interleukin 4 receptor and is seen within 48 hours after treatment. We examined signal transduction pathways used by the interleukin 4 receptor that may account for growth arrest of the cell line LUst but had no effect on another non-small cell lung cancer cell line, SK-MES-1. METHODS: Western blot analysis was performed on both LUst and SK-

MES-1 cell lines cultured in the presence of interleukin 4 (500 U/mL). Cells were lysed, protein extracted, and electroblotted; blots were then probed with murine monoclonal antibodies to specific intracellular proteins. RESULTS: Western blotting of the cell lines with antiphosphotyrosine antibody (4G10) demonstrated multiple (140 kd, 100-130 kd, and 65 kd) phosphoproteins seen only in the interleukin 4-treated LUst cell line and not observed in the SK-MES-1 cell lines. Immunoprecipitation and blotting of the LUst cell line with specific secondary antibodies demonstrated that the 140-kd phosphoprotein was the interleukin 4 receptor, the 130-kd phosphoprotein was Janus kinase 1, the 116-kd phosphoprotein was Janus kinase 3, and the 65-kd phosphoprotein was the interleukin 2 receptor gamma-chain. Specific binding was not observed in the non-small cell lung cancer cell line SK-MES-1, suggesting that a functional interleukin receptor gamma-chain was not present. Southern blotting with complementary DNA probes to interleukin 2 receptor gamma-chain confirmed the absence of this receptor on cell line SK-MES-1. CONCLUSIONS: These results suggest that non-small cell lung cancer cells may express functional cytokine receptors, including the interleukin 2 receptor gamma-chain commonly found in association with the lymphocyte interleukin 2 receptor. These receptors may be novel targets for directing cytokine-based immune therapy.

L43 ANSWER 8 OF 30 EMBASE  DUPLICATE 3

ACCESSION NUMBER: 1999038083 EMBASE Full-text
TITLE: Genetic induction of antigens and receptors as targets for cancer radiotherapy.
AUTHOR: Rogers B.E.; Garver R.I.; Grizzle W.E.; Buchsbaum D.J.
CORPORATE SOURCE: Dr. D.J. Buchsbaum, Department of Radiation Oncology, University of Alabama, 619 South 19th Street, Birmingham, AL 35233-6832, United States
SOURCE: Tumor Targeting, (1998) Vol. 3, No. 3, pp. 122-137. .
Refs: 56
ISSN: 1351-8488 CODEN: TUTAF
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 014 Radiology
022 Human Genetics
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 19990218
Last Updated on STN: 19990218

AB Limitations to radioimmunotherapy include bone marrow suppression due to the long serum half-life of radiolabeled monoclonal antibodies (mAbs) and poor tumor penetration of the large molecular weight mAb. In addition, low or variable expression of tumor-associated target antigens or receptors may lead to poor tumor localization of radiolabeled mAbs. Attempts to overcome these problems have included the use of radiolabeled peptides to improve tumor penetration and reduce bone marrow suppression and the use of biological response modifiers to increase target antigen expression. This report discusses a novel approach toward radiotherapy which combines gene transfer techniques, to induce high level tumor antigen or receptor expression, with radioligands that target the induced antigen or receptor. Major emphasis will be on the use of radiolabeled peptides for targeting induced receptors because the small molecular weight peptides may overcome tumor penetration and bone marrow suppression problems. Replication-deficient adenoviral vectors were constructed encoding the cDNA for carcinoembryonic antigen (CEA), thyrotropin-releasing hormone receptor (TRHr), epidermal growth factor receptor (EGFr), murine interleukin-4 receptor (mIL-4r), gastrin-releasing peptide receptor (GRPr), and the somatostatin receptor subtype (SSTr2). In vitro binding and in vivo tumor localization was observed

with radiolabeled anti-CEA mAbs, thyrotropin-releasing hormone, epidermal growth factor, IL- 4 fusion toxin, bombesin analogues, and octreotide analogues to cells infected with adenoviral vectors encoding the genes for CEA, TRHr, EGFr, mlL-4r, GRPr, and SSTr2, respectively. Also, methods to develop increased antigen or receptor expression using a replication enabling system will be discussed. Approaches to restrict antigen or receptor expression to the tumor through specific targeting of adenoviral vectors to the tumor or limiting the expression of protein to the tumor will be discussed. These methods should be useful for increasing the therapeutic efficacy of targeted radiotherapy.

L43 ANSWER 9 OF 30 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 1998012215 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 9348299
TITLE: Molecular characterization and functional analysis of murine interleukin 4 receptor allotypes.
AUTHOR: Schulte T; Kurrle R; Rollinghoff M; Gessner A
CORPORATE SOURCE: Institute of Clinical Microbiology and Immunology, University of Erlangen-Nurnberg, 91054 Erlangen, Germany.
SOURCE: The Journal of experimental medicine, (1997 Nov 3) Vol. 186, No. 9, pp. 1419-29.
Journal code: 2985109R. ISSN: 0022-1007.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF000304
ENTRY MONTH: 199711
ENTRY DATE: Entered STN: 19971224
Last Updated on STN: 20000303
Entered Medline: 19971120

AB The murine interleukin 4 receptor (IL-4R) exists as a transmembrane protein transducing pleiotropic IL-4 functions, or as soluble (s) IL-4-binding molecule with potent immunoregulatory effects. In this study we identified and characterized a murine IL-4R allotype. Sequence analysis of the IL-4R cDNA of BALB/c mice revealed 18 base substitutions leading to three extracellular and five cytoplasmic amino acid changes when compared with the published IL-4R sequence of C57BL/6 mice. Analyses with allotype-specific mAbs revealed that AKR/J and SJL/J mice possess the newly identified BALB/c IL-4R allotype whereas the IL-4Rs of C3H, CBA, DBA-2, and FVB/N mice are identical to that of the C57BL/6 mouse. The extracellular Thr49 to Ile substitution abrogates one N-glycosylation site in the naturally occurring BALB/c IL-4R as well as in the experimentally point mutated C57BL/6-T49I sIL-4R, and both molecules display a nearly threefold reduction in IL-4 -neutralizing activity compared to the C57BL/6 sIL-4R. In line with this, a significantly enhanced dissociation rate of IL-4 was detected for the BALB/c IL-4R allotype by surface plasmon resonance and in radioligand binding studies with IL-4R-transfected cell lines. These findings suggest that the altered ligand binding behavior of the newly described IL-4R allotype may influence the IL- 4 responsiveness, thus contributing to the diverse phenotypes of inbred mouse strains in IL-4-dependent diseases.

L43 ANSWER 10 OF 30 MEDLINE on STN
ACCESSION NUMBER: 97271795 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 9126705
TITLE: The production of soluble interleukin 4

receptors is preferentially regulated by the murine Th2 cell subset.

AUTHOR: Fernandez-Botran R; Chilton P M; Ma Y; Windsor J L; Street N E

CORPORATE SOURCE: Division of Immunology and Immunopathology, School of Medicine, University of Louisville, KY 40292, USA.

CONTRACT NUMBER: AI-34627 (NIAID)
CA-55266 (NCI)

SOURCE: Cytokine, (1997 Mar) Vol. 9, No. 3, pp. 166-77.
Journal code: 9005353. ISSN: 1043-4666.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals; AIDS

ENTRY MONTH: 199707

ENTRY DATE: Entered STN: 19970724
Last Updated on STN: 20000303
Entered Medline: 19970711

AB In order to understand how the endogenous production of soluble IL -4 receptors (sIL-4r) is regulated, the authors tested prototypic clones of Th1 and Th2 murine CD4+ T cell subsets for their ability to regulate their expression of sIL-4r. Results showed that although both types of clones produced low levels of sIL-4r under resting conditions, only the Th2 clones upregulated sIL-4r expression following antigenic stimulation. Inhibition of endogenous IL-4 with a neutralizing anti-IL-4 mAb had only a minor (approximately 20%) inhibitory effect on sIL-4r production by the Th2 cells, and addition of rIL-4 to Th1 cells resulted only in a modest two-fold increase in sIL-4r levels, suggesting that IL-4 is not the only factor that regulates sIL-4r production and that the ability of Th2 clones to upregulate sIL-4r expression can be relatively independent of IL-4. Indeed, the production of sIL-4r by Th2 cells was found to be regulated by cell contact and/or IL-1 mediated signals. Transcripts for both sIL-4r and mIL-4r were detected by RT-PCR on both resting and activated Th1 and Th2 cells, with the relative levels of expression being moderately higher in the Th2 clones. Moreover, the expression of sIL-4r-specific transcripts appeared to increase to a greater extent than those of mIL-4r after activation of Th2 cells with APCs, both in the presence and absence of antigen. Taken together, these results predict that increased sIL-4r production in vivo might be preferentially associated with Th2-type responses and indicate that even though the production of IL-4 and sIL-4r is mediated by the same cells (i.e. Th2 cells), the synthesis of sIL-4r can be regulated independently from that of IL-4 through alternative signals such as cell contact and/or IL-1. These properties may allow for changing ratios of sIL-4r to IL-4 and sIL-4r to mIL-4r during different phases of an immune response and are consistent with a regulatory role for sIL-4r on IL-4 activity in vivo.

L43 ANSWER 11 OF 30 MEDLINE on STN DUPLICATE 5

ACCESSION NUMBER: 1999035001 MEDLINE Full-text

DOCUMENT NUMBER: PubMed ID: 9816099

TITLE: Growth stimulation of human head and neck squamous cell carcinoma cell lines by interleukin 4.

AUTHOR: Myers J N; Yasumura S; Suminami Y; Hirabayashi H; Lin W c; Johnson J T; Lotze M T; Whiteside T L

CORPORATE SOURCE: Departments of Otolaryngology, Pathology, Molecular Genetics and Biochemistry, University of Pittsburgh, Pennsylvania 15213, USA.

CONTRACT NUMBER: 1RO1-CA63513-01 (NCI)
PO1-CA59371 (NCI)

SOURCE: Clinical cancer research : an official journal of the

American Association for Cancer Research, (1996 Jan) Vol. 2, No. 1, pp. 127-35.
Journal code: 9502500. ISSN: 1078-0432.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199902
ENTRY DATE: Entered STN: 19990223
Last Updated on STN: 19990223
Entered Medline: 19990210

AB Interleukin 4 (IL-4) has been reported recently to inhibit growth of acute lymphoblastic lymphoma, non-Hodgkin's lymphoma, melanoma, sarcoma, breast, gastric, colon, and renal tumor cell lines, and treatment of murine tumors with IL-4 gene-transduced cells has been therapeutically successful. Therefore, we sought to determine the effect of IL- 4 on the growth of human squamous cell carcinoma of the head and neck (SCCHN) cell lines. Growth of SCCHN cell lines incubated in the presence of various concentrations of IL-4 was measured in 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide colorimetric assays and by cell counts. Specific binding of IL-4 to SCCHN cells was demonstrated by flow cytometry with phycoerythrin-labeled IL-4, blocking studies with antibodies to IL-4, and using the radiolabeled ligand 125I-labeled IL-4. Reverse transcription PCR for IL-4 and IL-4 receptor (IL-4R) mRNA was performed. SCCHN tissue biopsies were examined by immunohistology and in situ hybridization for the presence of IL -4 protein and IL-4 mRNA in the tumor, respectively. In contrast to earlier reports, we observed growth stimulatory effects of IL-4 consistently in 6 of 13 SCCHN cell lines tested. Growth stimulation by IL-4 ranged from 20 to 200% of control ($P < 0.05$) and was IL- 4 dose dependent. The growth-promoting effect of IL- 4 was inhibited completely by incubation of tumor cells in the presence of antibodies specific for IL-4. Reverse transcription PCR analysis of mRNA obtained from the SCCHN cell lines and ELISA performed with SCCHN cell supernatants respectively indicated that the tumor cells did not transcribe or secrete IL- 4 actively. The SCCHN cell lines expressed 260-540 IL-4Rs/cell with a dissociation constant of 100 +/- 8 pM. SCCHN cell lines also contained IL-4R mRNA. Immunostaining of SCCHN tissue biopsies indicated that IL-4 may be produced and secreted within these tumors by tumor-infiltrating lymphocytes. In situ hybridization for IL-4 mRNA indicated the presence of positive cells in the tumor stroma. Our data suggest that IL-4 may regulate the growth of SCCHN cells by a paracrine mechanism. These data also indicate that immunotherapy with exogenous IL-4 or IL-4 gene therapy to treat head and neck cancer may not be effective, given the potential tumor growth-stimulatory effects of this cytokine.

L43 ANSWER 12 OF 30 EMBASE 

ACCESSION NUMBER: 95151664 EMBASE Full-text
DOCUMENT NUMBER: 1995151664
TITLE: Protein-tyrosine kinase-dependent activation of STAT transcription factors in interleukin-2- or interleukin-4-stimulated T lymphocytes.
AUTHOR: Brunn G.J.; Falls E.L.; Nilson A.E.; Abraham R.T.
CORPORATE SOURCE: Dept. of Immunology, Mayo Clinic, Guggenheim Bldg.,Rochester, MN 55905, United States
SOURCE: Journal of Biological Chemistry, (1995) Vol. 270, No. 19, pp. 11628-11635. .
ISSN: 0021-9258 CODEN: JBCHA3

COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 950607
Last Updated on STN: 950607

AB The proliferation of activated T lymphocytes is critically dependent on the binding of the T-cell growth factors, interleukin (IL)-2 and IL-4, to distinct but evolutionarily related cell surface receptors. Previous results suggest that the IL-2 receptor (IL-2R) and IL-4R are coupled to both overlapping and distinct intracellular signaling pathways in T lymphocytes. In this study, we demonstrate that activation of Janus tyrosine kinases (JAKs) and STAT transcription factors is rapidly induced by exposure of factor-dependent murine T-cell lines to IL-2 or IL-4. Both IL-2 and IL-4 stimulated the rapid activation of JAK1 and JAK3, whereas JAK2 activity was unaffected by either cytokine. These responses were accompanied by the appearance in cell nuclei of 3 DNA binding activities that recognized a high- affinity binding site for STAT factors. In transient transfection assays, this STAT factor target sequence conferred IL-2 and IL-4 inducibility on a synthetic luciferase reporter gene. Antibody supershifting experiments indicated that IL-2 induces the formation of STAT dimers containing STAT3 and STAT1α. Although IL- 4 also activated STAT1α, the major IL-A-induced STAT factor is not STAT3 and remains undefined. Pretreatment of the T-cells with the protein-tyrosine kinase inhibitor herbimycin A blocked both the nuclear translocation of STAT factors and STAT-dependent reporter gene transcription. Immunoblot analyses confirmed that cytoplasmic STAT3 was heavily phosphorylated on tyrosine in IL-2-stimulated cells, and that phosphorylated STAT3 appeared in the nuclei of these cells. These results indicate that identical JAKs and partially overlapping sets of STATs are activated by IL-2 and IL-4 in T lymphocytes.

L43 ANSWER 13 OF 30 MEDLINE on STN
ACCESSION NUMBER: 96049956 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 8548394
TITLE: Modulation of the immunoglobulin dysregulation in GvH- and SLE-like diseases by the murine IL-4 receptor (IL-4-R).
AUTHOR: Schorlemmer H U; Dickneite G; Kanzy E J; Enssle K H
CORPORATE SOURCE: Research Laboratories of Behringwerke AG, Marburg/Lahn, Germany.
SOURCE: Inflammation research : official journal of the European Histamine Research Society ... [et al.], (1995 Aug) Vol. 44 Suppl 2, pp. S194-6.
Journal code: 9508160. ISSN: 1023-3830.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199602
ENTRY DATE: Entered STN: 19960306
Last Updated on STN: 19960306
Entered Medline: 19960221

AB As has been reported previously, models of chronic graft-versus-host (GvH) and systemic lupus erythematosus (SLE)-like diseases are characterized by high IgE and IgG1 immunoglobulin (Ig) levels in the serum. An IL -4 induced pathological expansion of Th2 helper cells has been described for both disease models. Due to the immunopharmacological profile of soluble recombinant interleukin-4 receptor (IL-4-R) to bind

specifically the corresponding ligand IL-4 and thereby to modulate biological activity upon exogenous administration in various autoimmune disease models, we investigated the immunoregulatory activity of IL-4-R and anti-IL-4 monoclonal antibody (MAb) 11B11 on the development of SLE-like disease in MRL/lpr autoimmune mice and on chronic GvH reaction in BDF1 hybrid mice. Sensitized GvH-BDF1 hybrid mice and SLE in MRL/lpr autoimmune mice were treated in vivo with the IL- 4 antagonists to alter the pattern of serum Ig production and to modulate the disease process. These animals were followed for proteinuria, autoantibody production (anti-dsDNA), serum IgE, IgG1 and IgG2a levels, and the survival was monitored. Treatment of these diseased animals resulted in an improved survival rate, lowered the percentage of animals with lymphadenopathy and hepatosplenomegaly, reduced the levels of autoantibodies and inhibited proteinuria of the developing glomerulonephritis in both mouse strains, even in the established diseases. In both models the increase in total IgE and IgG1 levels in serum was strongly inhibited by the IL-4 antagonists, even under therapeutic conditions. But there was no inhibitory activity observed on the IgG2a serum levels.(ABSTRACT TRUNCATED AT 250 WORDS)

L43 ANSWER 14 OF 30 MEDLINE on STN
ACCESSION NUMBER: 96022606 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 8527165
TITLE: A potent human interleukin-4 antagonist stimulates the proliferation of murine cells expressing the human interleukin-4 binding chain.
AUTHOR: Davis I D; Treutlein H R; Friedrich K; Burgess A W
CORPORATE SOURCE: Ludwig Institute for Cancer Research, Melbourne Tumour Biology Branch, Royal Melbourne Hospital, Victoria, Australia.
SOURCE: Growth factors (Chur, Switzerland), (1995) Vol. 12, No. 1, pp. 69-83.
Journal code: 9000468. ISSN: 0897-7194.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199602
ENTRY DATE: Entered STN: 19960220
Last Updated on STN: 19970203
Entered Medline: 19960201

AB A single-amino-acid substitution mutant form of human interleukin-4 (hIL-4), Y124D.hIL-4, has been described previously as an antagonist of the effects of hIL-4 on various human cells. The murine T-cell leukemic cell line CT.h4S, which expresses the human IL-4 receptor, proliferates in response to both hIL-4 and murine IL- 4. Although Y124D.hIL-4 antagonizes the proliferative effects of hIL-4 on human phytohaemagglutinin-stimulated peripheral blood mononuclear cells, Y124D.hIL-4 is a potent stimulator for CT.h4S cells. Molecular modelling studies were performed to investigate the stability of different conformations of residue 124 as well as the efficiency of different molecular mechanics force fields in homology modelling. We suggest that the aspartate substitution alters the C-terminal end of the D-helix in such way that the analogue still binds to the human IL - 4 receptor alpha-chain and signals through the murine gamma c-chain. In contrast, the Y124D.hIL-4/IL- 4 receptor complex cannot signal through the human gamma c-chain.

L43 ANSWER 15 OF 30 EMBASE 

reserved on STN

ACCESSION NUMBER: 94102666 EMBASE Full-text
DOCUMENT NUMBER: 1994102666
TITLE: Subsets of murine lung fibroblasts express membrane-bound and soluble IL- 4 receptors: Role of IL-4 in enhancing fibroblast proliferation and collagen synthesis.
AUTHOR: Sempowski G.D.; Beckmann M.P.; Derdak S.; Phipps R.P.
CORPORATE SOURCE: School of Medicine and Dentistry, Univ. of Rochester Cancer Center, Box 704,Rochester, NY 14642, United States
SOURCE: Journal of Immunology, (1994) Vol. 152, No. 7, pp. 3606-3614. .
ISSN: 0022-1767 CODEN: JOIMA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
015 Chest Diseases, Thoracic Surgery and Tuberculosis
026 Immunology, Serology and Transplantation
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 940427
Last Updated on STN: 940427

AB The purpose of this study was to determine whether or not membrane-bound and soluble forms of IL-4 receptors are expressed by isolated subsets of murine lung fibroblasts and to evaluate the potential functional consequences of IL-4 receptor triggering. Recent studies demonstrate that IL -4- synthesizing Th2 cells and mast cells are present in increased numbers in the lung during inflammation and fibrosis, suggesting that IL-4 may play a regulatory role in these events. We hypothesize that pulmonary fibroblasts and subsets thereof are intimately involved in this inflammatory response and that IL- 4 is an active player in stimulating fibroblast collagen synthesis and hyperproliferation, creating a fibrotic environment in the lung. The fibroblast subsets used in these experiments differ not only in surface expression of the thymocyte-1 (Thy-1) Ag, but also in function and morphology. We now report the novel finding that IL-4 receptors are present at discordant levels on Thy-1+ and Thy-1- lung fibroblasts. IL-4R level and affinity were analyzed using a monoclonal anti-IL-4R Ab and equilibrium binding analysis with 125I-labeled IL-4. Reverse transcriptase PCR demonstrated the presence of mRNA for membrane-bound and soluble IL-4R. Lung fibroblast subsets secrete soluble IL-4R protein at dramatically different levels, as detected by an ELISA Thy-1+ and Thy-1- lung fibroblasts were treated with IL-4 to determine whether this cytokine was profibrotic Thy-1+ fibroblasts responded to IL-4 by proliferating and up-regulating collagen production. In contrast, Thy-1 fibroblasts proliferate to a lesser degree than Thy-1+ fibroblasts and were not stimulated to secrete increased levels of collagen. Overall, these results suggest that elevated levels of IL-4 at a site of injury could result in the development of fibrosis by enhancing fibroblast subset proliferation and collagen synthesis.

L43 ANSWER 16 OF 30 MEDLINE on STN DUPLICATE 6
ACCESSION NUMBER: 93271485 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 8499634
TITLE: Identification of a distinct low-affinity receptor for human interleukin-4 on pre-B cells.
AUTHOR: Fanslow W C; Spriggs M K; Rauch C T; Clifford K N; Macduff B M; Ziegler S F; Schooley K A; Mohler K M; March C J; Armitage R J
CORPORATE SOURCE: Immunex Research and Development Corp., Seattle, WA 98101.

SOURCE: Blood, (1993 Jun 1) Vol. 81, No. 11, pp. 2998-3005.
Journal code: 7603509. ISSN: 0006-4971.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199307
ENTRY DATE: Entered STN: 19930716
Last Updated on STN: 19980206
Entered Medline: 19930701

AB Biotinylated interleukin-4 (IL-4) was used to examine IL-4 receptor (IL-4R) expression on a range of human B-cell lines by flow cytometry. Using high concentrations of biotinylated IL-4, we have identified a novel low-affinity IL-4 receptor expressed at high levels on pre-B lines. Expression of this low-affinity receptor did not correlate with detected mRNA levels for the previously cloned receptor or with reactivity of two anti-human IL-4R monoclonal antibodies (MoAb). Radiolabeled IL -4 cross-linking studies using pre-B lines showed a doublet of 65 to 75 Kd in contrast to the 110- to 130-Kd molecule detected on cells expressing the cloned IL-4R. A soluble IL-4 binding protein (IL-4bp) was purified from the supernatants of three pre-B lines expressing the low-affinity receptor on their surface. IL-4bp could block both IL-4-mediated CD23 induction on tonsil B cells and IL-4-induced inhibition of proliferation of the pre-B line JM1. Partial N-terminal amino acid sequence was obtained from purified IL-4bp that confirmed this protein to be novel. A 12 amino acid peptide based on the IL-4bp sequence was used to produce a polyclonal antiserum that was reactive with purified IL-4bp, and also bound to the surface of pre-B cells but not to murine CTLL cells transfected with the human IL-4R. Blocking MoAb against the previously characterized high-affinity receptor inhibited IL-4 -mediated proliferation of hIL-4R+ CTLL cells but had no effect on IL-4-induced inhibition of JM1 cell proliferation, and only partially inhibited IL-4-mediated CD23 and sIgM induction and proliferation of tonsil B cells. The data presented here provide evidence for a novel cell-surface expressed low-affinity IL-4R that also exists as a biologically active soluble IL-4 binding protein.

L43 ANSWER 17 OF 30 MEDLINE on STN DUPLICATE 7
ACCESSION NUMBER: 93203592 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 8454851
TITLE: Recombinant soluble murine IL-4 receptor can inhibit or enhance IgE responses in vivo.
AUTHOR: Sato T A; Widmer M B; Finkelman F D; Madani H; Jacobs C A; Grabstein K H; Maliszewski C R
CORPORATE SOURCE: Department of Immunology, Immunex Research and Development Corp., Seattle, WA 98101.
SOURCE: Journal of immunology (Baltimore, Md. : 1950), (1993 Apr 1) Vol. 150, No. 7, pp. 2717-23.
Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199304
ENTRY DATE: Entered STN: 19930507
Last Updated on STN: 19980206
Entered Medline: 19930420

AB This study examines the effects of soluble IL-4R (sIL-4R) administration on IgE production in vivo by using an anti-IgD injection model. Anti-IgD-treated

mice were given various doses of sIL-4R or anti- IL-4 mAb over a 3-day period and serum IgE levels were determined by ELISA on day 9. The sIL-4R inhibited IgE production by up to 85%. Anti-IL-4 mAb administration resulted in comparable levels of inhibition at considerably lower doses. The disparity in efficacy between sIL-4R and anti-IL -4 mAb was likely the result of differences in the biodistribution and in vivo half-life of the two IL-4-binding proteins. The specificity of the sIL-4R inhibitory effect was assessed by mixing sIL-4R with various concentrations of IL-4 before injection. Exogenous IL-4 partially overcame the inhibitory effect of high-dose sIL-4R or anti-IL-4 mAb.
Unexpectedly, coadministration of suboptimal concentrations of anti- IL-4 mAb or sIL-4R with IL-4
resulted in superinduction of the IgE response. This stimulatory effect was dose dependent for both IL-4 and the IL- 4 cognates and was not seen in the absence of exogenous IL -4 over the entire concentration range tested for either sIL-4R or anti-IL mAb. The results indicate that sIL-4R can block IgE secretion by neutralizing endogenous IL-4. Furthermore, sIL-4R can enhance, in a dose-dependent manner, the biologic effects of exogenously administered IL-4, presumably by altering the biodistribution of the cytokine. These findings suggest two alternative applications for cytokine-binding proteins, i.e., 1) as antagonists of biologic activities of endogenously produced cytokines and, 2) as vehicles for cytokine delivery.

L43 ANSWER 18 OF 30 MEDLINE on STN
ACCESSION NUMBER: 94162515 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 8117935
TITLE: Characterisation of monoclonal antibodies to human IL-4: application in an IL-4 ELISA and differential inhibition of IL-4 bioactivity on B cells and T cells.
AUTHOR: van der Pouw Kraan T; Rensink I; Aarden L
CORPORATE SOURCE: Central Laboratory of the Netherlands Red Cross Blood, Transfusion Service (CLB), Amsterdam.
SOURCE: European cytokine network, (1993 Sep-Oct) Vol. 4, No. 5, pp. 343-9.
Journal code: 9100879. ISSN: 1148-5493.
PUB. COUNTRY: France
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199404
ENTRY DATE: Entered STN: 19940412
Last Updated on STN: 19940412
Entered Medline: 19940406

AB Five murine monoclonal antibodies, raised against E. coli derived human IL-4, were established. All mAb were also reactive with natural IL-4 . Competition ELISA experiments revealed that mAb 1,2 and 4 recognized a related epitope on IL-4. mAb 5 and mAb 6 recognized another epitope. Two non-competing mAb were used to develop a sandwich IL-4 ELISA. mAb 5 was used for coating and biotinylated mAb I was used as the second antibody. Intra- and interassay-coefficients were 3.3 and 10.1% respectively. The ELISA is specific for IL-4, rapid and sensitive (the detection limit is 2 pg/ml). The capacities of the antibodies to inhibit IL-4 activity were tested in B cell and T cell assays. All antibodies inhibited IL-4 dependent IgE production by human B lymphocytes. A similar inhibition of IL- 4 driven T cell proliferation by the antibodies was observed, with the exception that mAb 4 did not affect the activity of IL-4 on T cells. These results led to the suggestion that B cells make use of another (additional) IL- 4 receptor chain.

L43 ANSWER 19 OF 30 MEDLINE on STN DUPLICATE 8
ACCESSION NUMBER: 94043525 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 8227185
TITLE: Murine osteoblast interleukin 4 receptor expression: upregulation by 1,25 dihydroxyvitamin D3.
AUTHOR: Lacey D L; Erdmann J M; Tan H L; Ohara J
CORPORATE SOURCE: Department of Pathology, Jewish Hospital, Washington University, St. Louis, Missouri 63110.
CONTRACT NUMBER: AI26814 (NIAID)
SOURCE: Journal of cellular biochemistry, (1993 Oct) Vol. 53, No. 2, pp. 122-34.
Journal code: 8205768. ISSN: 0730-2312.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199312
ENTRY DATE: Entered STN: 19940117
Last Updated on STN: 19980206
Entered Medline: 19931221

AB The immune cytokine interleukin 4 has newly recognized effects on skeletal metabolism. While the interaction of many cells ultimately determines bone mass, we have examined the possibility that the osteoblast may be an IL-4 target in bone by characterizing IL-4 receptor (IL-4R) expression by MC3T3-E1 (MC3T3) murine osteoblastic cells. Based on 125I-IL-4 binding, MC3T3 cells express large numbers of IL-4 receptors (125I- IL-4 Bmax = 3,000-7,500 sites/cell, 125I-IL- 4 K = 13-40 pM) with an affinity similar to the IL- 4 receptor expressed by an IL-4 -responsive T cell line. Monoclonal anti-IL-4R antibodies (M1) blocked specific MC3T3 125I-IL-4 binding and MC3T3 total cell RNA contained full-length IL-4R mRNA as detected by reverse transcription DNA amplification utilizing IL-4R primers and Northern blot analysis. Functionally, IL-4 treatment of MC3T3 cells resulted in increased cellular proliferation (10-20%) and inhibition of alkaline phosphatase levels (20-40%). While parathyroid hormone (PTH) exposure did not influence IL-4R levels, vitamin D3 treatment augmented MC3T3 125I-IL-4 binding, in a time-dependent manner, up to threefold after a 24 h exposure with a metabolite specificity indicating the involvement of the vitamin D receptor. Equilibrium binding studies showed that the impact of 1,25 (OH)2 D3 on MC3T3 125I-IL-4 binding was due to an increased IL-4R Bmax. Cycloheximide treatment inhibited 1,25 (OH)2 D3-induced IL-4R upregulation, suggesting that protein synthesis was required. Furthermore, the steroid increased steady-state IL-4R mRNA levels in both a time- and concentration-dependent manner. The IL-4R message half-life was not altered by 1,25 (OH)2 D3, suggesting that increased IL-4R mRNA expression resulted from increased IL-4R gene transcription. Taken together, these findings raise the possibility that IL-4's influence on mineral metabolism could be mediated by osteoblasts and that the effectiveness of this cytokine may be influenced by vitamin D3's impact on IL-4R expression.

L43 ANSWER 20 OF 30 MEDLINE on STN
ACCESSION NUMBER: 93139258 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 8423237
TITLE: Expression of high affinity interleukin-4 receptors on human renal cell carcinoma cells and inhibition of tumor cell growth in vitro by interleukin-4.
AUTHOR: Obiri N I; Hillman G G; Haas G P; Sud S; Puri R K

CORPORATE SOURCE: Division of Cytokine Biology, Food and Drug Administration, Bethesda, Maryland 20892.
SOURCE: The Journal of clinical investigation, (1993 Jan) Vol. 91, No. 1, pp. 88-93.
Journal code: 7802877. ISSN: 0021-9738.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199302
ENTRY DATE: Entered STN: 19930312
Last Updated on STN: 19980206
Entered Medline: 19930224

AB Previously, Puri et al. (Puri, R. K., M. Ogata, P. Leland, G. M. Feldman, D. Fitzgerald, and I. Pastan. 1991. Cancer Res. 51:3011-3017) have demonstrated that murine sarcoma and colon adenocarcinoma cells express high affinity interleukin-4 receptors (IL-4R) which are internalized after binding to a chimeric ligand consisting of IL-4 and Pseudomonas exotoxin. In the present study, we have tested primary cultures of human renal cell carcinoma (RCC) cells, generated from tumor specimens obtained after nephrectomy, for the expression of IL-4R and their modulation by IL-4. By using iodinated IL-4 in a receptor binding assay, we observed that renal cell carcinoma cells expressed a single class of high affinity IL-4R ranging from 1,425 +/- 207 (mean +/- SEM) to 3,831 +/- 299 (mean +/- SEM) IL-4R molecules/cell with a Kd ranging from 112 +/- 11 pM to 283 +/- 71 pM. Northern blot analysis for IL-4R gene expression, performed with a cDNA probe to IL-4R, revealed that all RCC cells exhibited a single mRNA species of 4 kb. IL-4 downregulated the surface expression of IL-4R on one RCC tumor cell line. The function of IL-4R expression on RCC tumor cells was further determined by investigating the effect of IL-4 on tumor cell growth in vitro and comparing it with IL-4 effect on growth of normal fibroblast and endothelial cell lines. Tumor cell growth, as measured by [3H]thymidine incorporation, was inhibited by IL-4 from 20 to 68% in a dose-dependent manner. A neutralizing antibody to human IL-4 was able to reverse the growth inhibitory effect of IL-4. Normal human fibroblast and endothelial cell lines also expressed high affinity IL-4R, however, IL-4 did not inhibit their growth in vitro. In fact, IL-4 caused modest stimulation of their growth. Taken together, our findings can help develop strategies for the treatment of RCC in which IL-4R may be used as a target for IL- 4 itself, for IL-4 toxin therapy or, alternatively, in gene therapy.

L43 ANSWER 21 OF 30 MEDLINE on STN DUPLICATE 9
ACCESSION NUMBER: 93318108 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 8327860
TITLE: Adoptive transfer of low numbers of CD4+ T cells into SCID mice chronically treated with soluble IL-4 receptor does not prevent engraftment of IL-4-producing T cells.
AUTHOR: Rudolphi A; Enssle K H; Claesson M H; Reimann J
CORPORATE SOURCE: Institute of Microbiology, University of Ulm, Germany.
SOURCE: Scandinavian journal of immunology, (1993 Jul) Vol. 38, No. 1, pp. 57-64.
Journal code: 0323767. ISSN: 0300-9475.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199308
ENTRY DATE: Entered STN: 19930820
Last Updated on STN: 19980206

Entered Medline: 19930812

AB After intravenous injection of 10(5) purified, lymph node (LN)-derived dm2 (H-2d/Ld-) CD4+ T cells into young C.B-17 scid/scid (severe combined immunodeficiency, SCID) mice (H-2d/Ld+), the transplanted Ld-T cells show a selective pattern of engraftment: they repopulate the spleen, the lamina propria of the small intestine and the mesenteric LN (but not other peripheral LN) of the immunodeficient host. CD4+ cells repopulating different lymphoid organs of the SCID recipient mice produce interleukin-2 (IL-2) and interleukin-4 (IL-4) in response to polyclonal stimulation in vitro. Some evidence has recently been provided that cytokines (e.g. IL-4) present at the site of antigen stimulation in vivo decisively influence the pattern of cytokines expressed by T cells activated at these sites. We therefore asked if neutralization of IL-4 by chronic treatment of SCID mice with high doses of recombinant soluble IL-4 receptor (sIL-4R) changes the IL-4 or IL-2 expression pattern of CD4+ T cells adoptively transferred into young SCID recipients. Transplanted SCID mice were chronically treated with two different, recombinant murine sIL-4R proteins. The experimental series further included groups of transplanted SCID mice treated with a recombinant human sIL-4R protein (which does not bind murine IL-4), treated with the anti-murine IL-4 monoclonal antibody (MoAb) 11B11, or non-treated. Transplanted SCID mice treated with the recombinant murine sIL-4R protein preparations displayed detectable sIL-4R serum levels, which demonstrates that the substitution therapy could maintain neutralizing serum levels of anti-IL-4 activity in SCID mice. By contrast, no serum sIL-4R levels were detectable in the sensitive ELISA readout in transplanted SCID mice which were non-treated, treated with the MoAb 11B11, or treated with the recombinant humans sIL-4R protein. The efficiency and the pattern of CD4+ T-cell engraftment, and the lymphokine-producing phenotype of the engrafted dm2 CD4+ cells, was not affected by the continuous IL-4-neutralizing treatment of mice with either the MoAb 11B11 or the soluble IL-4R preparations. Hence, in contrast to the published evidence of the dramatic effect of IL-4 on the lymphokine-producing phenotype of CD4+ T cells stimulated in vitro or in vivo, the chronic suppression in vivo of IL-4 activity (by either different sIL4-R protein constructs, or by the anti-IL-4 MoAb 11B11) did not lead to preferential engraftment of Th1-type CD4+ T cells after adoptive transfer of CD4+ T-cell populations into an immunodeficient recipient.

L43 ANSWER 22 OF 30 MEDLINE on STN DUPLICATE 10

| | |
|---|---|
| ACCESSION NUMBER: | 91235210 MEDLINE Full-text |
| DOCUMENT NUMBER: | PubMed ID: 2032239 |
| TITLE: | Expression of high-affinity interleukin 4 receptors on murine sarcoma cells and receptor-mediated cytotoxicity of tumor cells to chimeric protein between interleukin 4 and Pseudomonas exotoxin. |
| AUTHOR: | Puri R K; Ogata M; Leland P; Feldman G M; FitzGerald D; Pastan I |
| CORPORATE SOURCE: | Division of Cytokine Biology, Food and Drug Administration, Bethesda, Maryland 20892. |
| SOURCE: | Cancer research, (1991 Jun 1) Vol. 51, No. 11, pp. 3011-7. Journal code: 2984705R. ISSN: 0008-5472. |
| PUB. COUNTRY: | United States |
| DOCUMENT TYPE: | Journal; Article; (JOURNAL ARTICLE) |
| LANGUAGE: | English |
| FILE SEGMENT: | Priority Journals |
| ENTRY MONTH: | 199106 |
| ENTRY DATE: | Entered STN: 19910714 Last Updated on STN: 19980206 |

Entered Medline: 19910621

AB The presence of interleukin 4 receptor (IL-4R) on methylcholanthrene (MCA-106, MCA-102, and MC-38)- and viral DNA (G-2TS and 14-2TS)-induced murine sarcoma cells was demonstrated. MCA-106 tumor cells express about 500 to 1348 (median, 800) interleukin 4 (IL-4) binding sites/cell with a dissociation constant (Kd) of 115 +/- 26 pM (mean +/- SD, n = 4). By Northern blot analysis, tumor cells exhibited a single mRNA species of 3.9 kilobases. Other murine sarcoma (MCA-102), colon adenocarcinoma (MC-38), G-2TS, and 14-2TS tumor cells express low numbers of IL-4R. By immunoperoxidase staining, 81 to 92% of the cells from fresh MCA-106 tumors were positive for IL-4 receptors, while only 7 to 10% of tumor-infiltrating cells were Thy 1.2 and less than 1% Mac-1 positive. Using a chimeric protein composed of IL-4 and Pseudomonas exotoxin (IL -4-PE40), we observed that IL-4-PE40 was cytotoxic (determined by inhibition of protein synthesis by [3H]leucine uptake) to MCA-106 tumor cells in a dose-dependent manner. A nonchimeric protein (PE40) that cannot bind to the IL-4R did not inhibit protein synthesis in tumor cells. A chimeric mutant protein (IL4-PE40 asp553) that can bind to IL-4 receptors but does not have the capability to inhibit protein synthesis was not cytotoxic to tumor cells. These studies strongly suggest that IL-4R on murine MCA-106 sarcoma cells is internalized when occupied by IL- 4 PE40. Furthermore, a neutralizing antibody (11B11) to IL-4 completely abolished the protein synthesis-inhibitory activity of IL-4-PE40. G-2TS tumor cells which expressed low numbers of IL-4 receptors were not vulnerable to cytotoxicity by IL- 4-PE40. Taken together, these data suggest that IL- 4 receptor may be a target for IL-4 -toxin therapy.

L43 ANSWER 23 OF 30 MEDLINE on STN DUPLICATE 11

ACCESSION NUMBER: 91341427 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 1875167
TITLE: Evidence that natural murine soluble interleukin 4 receptors may act as transport proteins.
AUTHOR: Fernandez-Botran R; Vitetta E S
CORPORATE SOURCE: Department of Microbiology, University of Texas Southwestern Medical Center, Dallas 75235.
CONTRACT NUMBER: AI-11851 (NIAID)
AI-21229 (NIAID)
SOURCE: The Journal of experimental medicine, (1991 Sep 1) Vol. 174, No. 3, pp. 673-81.
Journal code: 2985109R. ISSN: 0022-1007.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199109
ENTRY DATE: Entered STN: 19911013
Last Updated on STN: 20000303
Entered Medline: 19910926

AB The present studies were undertaken to determine whether the interleukin 4 binding proteins (IL-4BPs) previously identified in the biological fluids of mice are soluble forms of IL-4Rs. We also studied the binding properties of IL-4BPs in order to gain insight into their physiological role in vivo. Affinity-purified IL-4BPs and recombinant soluble IL-4Rs generated similar one-dimensional (Cleveland) peptide maps after digestion with either Staphylococcus aureus V8 protease or trypsin, indicating structural similarities. Furthermore, a rat mAb directed against the murine IL-4Rs immunoprecipitated the IL-4BPs and completely inhibited binding of 125I-IL-4 to a purified preparation of IL-4BPs. Taken together these data indicate that the IL-4BPs are soluble IL-4Rs.

At 4 degrees C the IL-4BPs competitively inhibited the binding of IL-4 to membrane IL-4Rs but their ability to prevent binding of IL- 4 to cells at 37 degrees C, at the same concentrations, was significantly reduced. Kinetic binding studies of soluble IL-4BPs vs. membrane IL-4Rs disclosed important differences in their rates of dissociation from IL-4. Whereas dissociation at 4 degrees C was slow for both, dissociation of IL-4 from IL-BPs at 37 degrees C was considerably faster (t 1/2 of 2 min) than dissociation of IL-4 from membrane IL-4Rs (t 1/2 of approximately 69 min). Temperature-dependent changes in dissociation kinetics were reversible, and could not be accounted for by either inactivation of the IL-4BPs at 37 degrees C or receptor internalization. Additional experiments also demonstrated that when IL-4BPs bind to IL-4 at 37 degrees C, the IL-4 /IL-4BPs complex can rapidly dissociate, allowing IL-4 to bind to membrane IL-4Rs. In addition, binding of IL-4 by the IL-4BPs protects IL-4 from proteolytic degradation. Taken together, these results suggest that the IL-4BPs are naturally occurring forms of soluble IL-4Rs and that some of their properties (fast dissociation kinetics and protection of IL-4 from proteolysis) are consistent with a potential role as carrier proteins for IL-4 in the circulation.

L43 ANSWER 24 OF 30 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1990:606219 CAPLUS Full-text
DOCUMENT NUMBER: 113:206219
TITLE: Recombinant mammalian interleukin-4 receptors for regulation of immune response
INVENTOR(S): Cosman, David J.; Park, Linda; Mosley, Bruce; Beckmann, Patricia; March, Carl J.; Idzerda, Rejean
PATENT ASSIGNEE(S): Immunex Corp., USA
SOURCE: Eur. Pat. Appl., 37 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| EP 367566 | A1 | 19900509 | EP 1989-311244 | 19891031 |
| EP 367566 | B1 | 19970514 | | |
| R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE | | | | |
| WO 9005183 | A1 | 19900517 | WO 1989-US4076 | 19890918 |
| W: AU, BR, DK, FI, KR, NO | | | | |
| AU 8944113 | A1 | 19900528 | AU 1989-44113 | 19890918 |
| AU 643427 | B2 | 19931118 | | |
| IL 91705 | A1 | 19981227 | IL 1989-91705 | 19890920 |
| CA 1340761 | A1 | 19990921 | CA 1989-614293 | 19890928 |
| ZA 8908014 | A | 19901031 | ZA 1989-8014 | 19891023 |
| JP 02215385 | A2 | 19900828 | JP 1989-284660 | 19891031 |
| JP 2744821 | B2 | 19980428 | | |
| AT 153068 | E | 19970515 | AT 1989-311244 | 19891031 |
| ES 2103706 | T3 | 19971001 | ES 1989-311244 | 19891031 |
| DK 9100784 | A | 19910430 | DK 1991-784 | 19910429 |
| DK 175583 | B1 | 20041213 | | |
| FI 106044 | B1 | 20001115 | FI 1991-2064 | 19910429 |
| NO 9101713 | A | 19910430 | NO 1991-1713 | 19910430 |
| NO 309000 | B1 | 20001127 | | |

PRIORITY APPLN. INFO.:

| | | |
|---|---|---|
| US 1988-265047 | A | 19881031 |
| US 1989-319438 | A | 19890302 |
| US 1989-326156 | A | 19890320 |

US 1989-370924 A 19890623
WO 1989-US4076 A 19890918

AB The cDNAs encoding murine and human interleukin- 4 (IL-4) receptors are cloned and
expressed in mammalian cells. These receptors can be used to modulate the immune response in mammals. The cDNAs encoding full-length receptors and truncated, soluble receptors were isolated from murine 7B9 or CTLL cells. From human peripheral blood lymphocytes cDNA encoding full-length receptors were cloned and cDNAs encoding soluble receptors were constructed. Expression vectors containing these cDNAs were prepared COS cells containing the vectors produced membrane-bound or soluble receptors. Soluble IL- 4 receptor suppressed the host vs. graft response in mice (popliteal lymph node assay).

L43 ANSWER 25 OF 30 MEDLINE on STN DUPLICATE 12
ACCESSION NUMBER: 90257336 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 1692858
TITLE: Monoclonal antibodies block murine IL-4 receptor function.
AUTHOR: Beckmann M P; Schooley K A; Gallis B; Vanden Bos T; Friend D; Alpert A R; Raunio R; Prickett K S; Baker P E; Park L S
CORPORATE SOURCE: Immunex Corporation, Seattle, WA 98101.
SOURCE: Journal of immunology (Baltimore, Md. : 1950), (1990 Jun 1) Vol. 144, No. 11, pp. 4212-7.
Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199006
ENTRY DATE: Entered STN: 19900720
Last Updated on STN: 19980206
Entered Medline: 19900628

AB IL-4 is a cytokine which can induce B-lymphocyte proliferation, increase cell-surface Ia expression, and induce some activated B cells to differentiate and begin to secrete IgE. IL -4 binds specifically to a cell-surface receptor (IL-4R) on cells from a variety of lineages including T and B cells. In general both primary cells and in vitro cell lines express less than 5000 receptors per cell. Utilizing a subclone of the cytotoxic T cell line CTLL-2 expressing a high level of IL-4R, mAb against the murine IL-4R were prepared. Two mAb have been identified which have different properties. These antibodies, designated M1 and M2, recognize sequences specific to the murine IL-4R. Immunoprecipitation studies with M1 and M2 on CTLL-2 cells have identified the receptor as a Mr = 145,000 cell-surface protein. Similar results have been obtained with the recently isolated full length murine IL-4R cDNA expressed in COS-7 cells. In addition the antibodies are capable of inhibiting IL-4 binding. One antibody, M1, is also a potent inhibitor of IL-4-induced proliferation. These antibodies will be useful in dissecting a wide array of activities attributed to IL-4.

L43 ANSWER 26 OF 30 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1991:4644 CAPLUS Full-text
DOCUMENT NUMBER: 114:4644
TITLE: Cross-talk between B cell surface immunoglobulin and interleukin 4 receptors: the role of protein kinase C and calcium-mediated signals
AUTHOR(S): Klaus, Gerry G. B.; Harnett, Margaret M.

CORPORATE SOURCE: Natl. Inst. Med. Res., London, NW7 1AA, UK
SOURCE: European Journal of Immunology (1990), 20(10), 2301-7
CODEN: EJIMAF; ISSN: 0014-2980
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A well-known property of IL 4 is its capacity to synergize with low concns. of anti-Ig antibodies to induce B cells to synthesize DNA. Crosslinking of surface Ig receptors stimulates phosphoinositide hydrolysis, with consequent production of two signals: the elevation of intracellular Ca2+ levels and activation of protein kinase C (PKC). Little is known about the second messengers utilized by interleukin (IL) 4 receptors. In this study the relative contributions were investigated of the two signals emanating from the ligation of surface Ig receptors to the synergistic activation of B cells by IL 4. IL 4 plus carefully titrated concns. of PKC-activating phorbol esters induce cell cycle entry of virtually all murine B cells and substantial levels of DNA synthesis. Ca2+ ionophores, in contrast do not act as co-mitogens with IL 4. However, a critical concentration of ionomycin further enhanced DNA synthesis induced by phorbol esters plus IL 4. These results suggest that PKC activation alone is sufficient to synergize with IL 4 in inducing B cells to enter cell cycle. However, the co-mitogenic effects of anti-Ig and IL 4 are evidently also dependent on Ca2+ signals. This interpretation is supported by the findings that cyclosporin, which abrogates the activation of lymphocytes by Ca2+-dependent stimuli, inhibits B cell proliferation induced by anti-Ig plus IL 4, but not the response to PBu2 plus IL 4.

L43 ANSWER 27 OF 30 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1990:589485 CAPLUS Full-text
DOCUMENT NUMBER: 113:189485
TITLE: Induction of B cell activities by interleukin 4 is inhibited by a receptor-specific monoclonal antibody in vitro
AUTHOR(S): Maliszewski, Charles R.; Sato, Timothy A.; Vanden Bos, Tim; Beckmann, M. Patricia; Grabstein, Kenneth H.
CORPORATE SOURCE: Dep. Immunol., Immunex Corp., Seattle, WA, 98101, USA
SOURCE: European Journal of Immunology (1990), 20(8), 1735-40
CODEN: EJIMAF; ISSN: 0014-2980
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effects of interleukin (IL) 4 on B cell growth and differentation are mediated through binding of IL 4 to a specific cell surface receptor. The murine T cell IL 4 receptor (IL 4R) has recently been cloned and monoclonal antibodies (mAb) which bind specifically to the IL 4R have been developed. The ability of two of these anti-IL 4R mAb (M1 and M2) to inhibit IL 4-induced B cell functions in vitro was examined The M1 mAb inhibited the ability of IL 4 to induce B cell proliferation in a dose-related fashion. The inhibition was specific for proliferation induced by IL 4 in that the antibody did not affect induction of proliferation by IL 1. Similarly, M1 inhibited IL 4-dependent B cell differentiation as measured by induction of IgG1 and IgE secretion, decreased IgG3 secretion, increased Ia expression, and increased FcεR (CD23) expression. In contrast, the anti-IL 4R-specific mAb M2 had no effect upon any of these activities. The ability of M1 but not M2 to inhibit IL 4-induced B cell growth and differentiation correlated with the inhibition of binding of radiolabeled IL 4 by M1.

L43 ANSWER 28 OF 30 MEDLINE on STN DUPLICATE 13
ACCESSION NUMBER: 91370704 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 2104233

TITLE: A soluble form of the interleukin 4 receptor in biological fluids.
AUTHOR: Fanslow W C; Clifford K; VandenBos T; Teel A; Armitage R J; Beckmann M P
CORPORATE SOURCE: Immunex Corporation, Seattle, Washington 98101.
SOURCE: Cytokine, (1990 Nov) Vol. 2, No. 6, pp. 398-401.
Journal code: 9005353. ISSN: 1043-4666.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199110
ENTRY DATE: Entered STN: 19911108
Last Updated on STN: 19980206
Entered Medline: 19911018

AB Murine biological fluids and murine cell culture supernatants were analyzed for the presence of soluble murine interleukin 4 receptor (sIL4R) with the use of two monoclonal antibodies directed against the receptor. Mouse urine, serum, ascitic fluid, and cell culture supernatants contained varying levels of immunoreactive protein. All of the immunoreactive protein possessed interleukin 4 (IL 4) binding activity.
Following partial purification of ascitic fluid a protein was isolated that binds IL 4 with high affinity. This data is consistent with the fact that murine biological fluids contain a soluble version of the murine IL 4 receptor that arises via secretion of the soluble receptor and/or via shedding of the extracellular portion of the full-length receptor from the cell surface.

L43 ANSWER 29 OF 30 MEDLINE on STN DUPLICATE 14
ACCESSION NUMBER: 89264593 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 2786209
TITLE: Cross-linking of interleukin 4 to surface molecules on murine T and B lymphocytes.
AUTHOR: Fernandez-Botran R; Uhr J W; Vitetta E S
CORPORATE SOURCE: Department of Microbiology, University of Texas Southwestern Medical Center, Dallas 75235.
CONTRACT NUMBER: AI-11851 (NIAID)
AI-1278 (NIAID)
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1989 Jun) Vol. 86, No. 11, pp. 4235-9.
Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198907
ENTRY DATE: Entered STN: 19900309
Last Updated on STN: 19980206
Entered Medline: 19890712

AB Interleukin 4 (IL-4) is a T-cell derived lymphokine with multiple activities on a variety of cells. An intriguing feature of the different IL-4-mediated activities is their requirements for markedly different concentrations of IL-4 even on the same cell population. To gain some insight into the phenomenon, we have analyzed the structure of IL -4-binding proteins on T and B cells by cross-linking different concentrations of 125I-labeled IL- 4 (125I-IL-4) to cells. Cross-linking of 125I-IL-4 at relatively low concentrations in the presence of the cross-linking agent 3,3'-dithiobis(propionic acid hydroxysuccinimide ester) resulted in the detection of the previously described 60- to 75-kDa protein.

At higher 125I-IL- 4 concentrations, however, an additional molecule of 105 kDa was observed. Cross-linking of 125I-IL-4 to both molecules was specific; it was inhibited by the presence of a 50-fold excess of either unlabeled IL-4 or monoclonal anti- IL-4 antibody. Furthermore, considerable size heterogeneity of the IL-4-binding proteins was evident in different cell populations. These results suggest that IL-4 receptors might have a more complex structure than originally reported and/or that high concentrations of IL-4 might induce interactions of the previously described IL-4 receptor (60-75 kDa) with a 105-kDa molecule. Hence, it is possible that IL-4 might generate a different signal at high concentrations through interaction of its receptor with another membrane molecule.

L43 ANSWER 30 OF 30 MEDLINE on STN DUPLICATE 15

ACCESSION NUMBER: 89264588 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 2657746
TITLE: Cytotoxic activity of a recombinant fusion protein between interleukin 4 and Pseudomonas exotoxin.
AUTHOR: Ogata M; Chaudhary V K; FitzGerald D J; Pastan I
CORPORATE SOURCE: Laboratory of Molecular Biology, National Institutes of Health, Bethesda, MD 20892.
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1989 Jun) Vol. 86, No. 11, pp. 4215-9.
Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198907
ENTRY DATE: Entered STN: 19900309
Last Updated on STN: 20020420
Entered Medline: 19890712

AB A recombinant chimeric toxin in which the cell binding domain of Pseudomonas exotoxin (PE) was replaced by murine interleukin 4 (IL-4) was produced in Escherichia coli. This chimeric protein, IL-4 -PE40, was cytotoxic to murine IL-4 receptor-bearing cell lines but had little effect on human cell lines lacking receptors capable of binding murine IL-4. A mutant form of IL-4-PE40 (termed IL-4-PE40 asp553) with very low ADP-ribosylating activity displayed mitogenic activity similar to that of IL-4 rather than cytotoxic activity. Because the cytotoxic effects of IL-4-PE40 were blocked by excess IL-4 or by neutralizing antibody to IL -4 (11B11), we conclude that the cytotoxic effect of IL -4-PE40 is specifically mediated through IL-4 receptors. IL-4-PE40 could be a useful reagent for specific elimination of cells bearing IL-4 receptors.

L44 36 FILE MEDLINE
L45 61 FILE BIOSIS
L46 25 FILE EMBASE
L47 41 FILE CAPLUS

TOTAL FOR ALL FILES
L48 163 MOSLEY B?/AU

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=> s l48 not l37
L49          36 FILE MEDLINE
L50          61 FILE BIOSIS
L51          25 FILE EMBASE
L52          40 FILE CAPLUS

TOTAL FOR ALL FILES
L53         162 L48 NOT L37

=> s l27 and inhibit?
L54          55 FILE MEDLINE
L55          41 FILE BIOSIS
L56          60 FILE EMBASE
L57         122 FILE CAPLUS

TOTAL FOR ALL FILES
L58         278 L27 AND INHIBIT?

=> s l58 and l48
L59           0 FILE MEDLINE
L60           0 FILE BIOSIS
L61           0 FILE EMBASE
L62           0 FILE CAPLUS

TOTAL FOR ALL FILES
L63           0 L58 AND L48

=> s l58 and cell
L64          52 FILE MEDLINE
L65          40 FILE BIOSIS
L66          57 FILE EMBASE
L67         111 FILE CAPLUS

TOTAL FOR ALL FILES
L68         260 L58 AND CELL

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     (FILE 'HOME' ENTERED AT 15:01:41 ON 31 MAR 2006)

     FILE 'REGISTRY' ENTERED AT 15:02:26 ON 31 MAR 2006
                E INTERLEUKIN 4/CN 5
L1           243 S INTERLEUKIN 4 ?/CN
                E INTERLEUKIN 4 RECEPTOR/CN
L2            62 S INTERLEUKIN 4 RECEPTOR ?/CN

     FILE 'MEDLINE, BIOSIS, EMBASE, CAPLUS' ENTERED AT 15:04:37 ON 31 MAR 2006
L3         33794 FILE MEDLINE
L4         27091 FILE BIOSIS
L5         26198 FILE EMBASE
L6         22783 FILE CAPLUS
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L7        109866 S (L1 OR INTERLEUKIN 4 OR HISTOCOMPATIBILITY ANTIGENS CLASS II
L8         42794 FILE MEDLINE
L9         32534 FILE BIOSIS
L10        29170 FILE EMBASE
L11        27786 FILE CAPLUS
     TOTAL FOR ALL FILES
L12       132284 S L7 OR IL-4
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L13          879 FILE MEDLINE
L14         1356 FILE BIOSIS
L15         1383 FILE EMBASE
L16         1548 FILE CAPLUS
     TOTAL FOR ALL FILES
L17         5166 S L2 OR INTERLEUKIN 4 RECEPTOR OR IL-4(W)(R OR RECEPTOR) OR CD1
L18          261 FILE MEDLINE
L19          271 FILE BIOSIS
L20          435 FILE EMBASE
L21          484 FILE CAPLUS
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L22         1451 S (ANTIBOD? OR MONOCLONAL ANTIBOD? OR MAB) AND L12 AND L17
L23           92 FILE MEDLINE
L24           78 FILE BIOSIS
L25          128 FILE EMBASE
L26          204 FILE CAPLUS
     TOTAL FOR ALL FILES
L27          502 S L22 AND BIND?
L28           27 FILE MEDLINE
L29           21 FILE BIOSIS
L30           29 FILE EMBASE
L31           27 FILE CAPLUS
     TOTAL FOR ALL FILES
L32          104 S MURINE AND L27
L33           19 FILE MEDLINE
L34           13 FILE BIOSIS
L35           18 FILE EMBASE
L36           19 FILE CAPLUS
     TOTAL FOR ALL FILES
L37           69 S L32 AND (AMINO ACID OR PROTEIN)
L38            0 FILE MEDLINE
L39            0 FILE BIOSIS
L40            0 FILE EMBASE
L41            0 FILE CAPLUS
     TOTAL FOR ALL FILES
L42            0 S INIHIBT? AND L37
L43           30 DUP REM L37 (39 DUPLICATES REMOVED)
L44           36 FILE MEDLINE
L45           61 FILE BIOSIS
L46           25 FILE EMBASE
L47           41 FILE CAPLUS
     TOTAL FOR ALL FILES
L48          163 S MOSLEY B?/AU
L49           36 FILE MEDLINE
L50           61 FILE BIOSIS
L51           25 FILE EMBASE
L52           40 FILE CAPLUS
     TOTAL FOR ALL FILES
L53          162 S L48 NOT L37
L54           55 FILE MEDLINE
L55           41 FILE BIOSIS
L56           60 FILE EMBASE
L57          122 FILE CAPLUS
     TOTAL FOR ALL FILES
L58          278 S L27 AND INHIBIT?
L59            0 FILE MEDLINE
L60            0 FILE BIOSIS
L61            0 FILE EMBASE
L62            0 FILE CAPLUS
     TOTAL FOR ALL FILES
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L63             0 S L58 AND L48
L64            52 FILE MEDLINE
L65            40 FILE BIOSIS
L66            57 FILE EMBASE
L67           111 FILE CAPLUS
     TOTAL FOR ALL FILES
L68           260 S L58 AND CELL

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COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                   147.37     158.86

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                       ENTRY    SESSION
CA SUBSCRIBER PRICE                                    -3.75      -3.75

STN INTERNATIONAL LOGOFF AT 15:14:22 ON 31 MAR 2006
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 656 S MOSLEY B/AU OR PARK L/AU OR COSMAN D/AU OR MARCH C/AU OR IDZE
L22         1576 S ((INTERLEUKIN-4 RECEPTOR) OR (IL-4 RECEPTOR) OR IL-4R) AND AN
L23            1 S L21 AND L22
L24          416 DUP REM L21 (240 DUPLICATES REMOVED)
L25          843 DUP REM L22 (733 DUPLICATES REMOVED)
L26           40 S L25 AND PY<=1990
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